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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| CROUCH, DEBORAH | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

DATE MAILED: 08/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/809,738 | STICE, STEVEN | |
| | Examiner | Art Unit | |
| | Deborah Crouch, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-30 are pending.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a cloned nonprimate mammalian NT embryo comprising introducing a donor metaphase cell or nucleus from a donor metaphase cell and a method of producing a cloned nonprimate mammal comprising introducing a donor metaphase cell or nucleus from a donor metaphase cell, does not reasonably provide enablement for a method of producing a cloned nonhuman mammalian NT embryo or a method of producing a cloned nonhuman mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The term "donor genetic material" is not enabled for its full breadth. The donor genetic material needs to be in the form of a nucleus or cell. As written the claims encompass the introduction of separate chromosomes. It is unpredictable that a chromatin mass or individual chromosomes will support term development.

The art at the time of filing taught the cloning of monkeys, a primate, by nuclear transfer had been successful when embryonic cells were the nuclear donor, but not when somatic cells were used as nuclear donor (Mitalipov, abstract). Mitalipov further states, clearly, that somatic cell cloning, as is part of the present methods, has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Simerly, states that in rhesus monkey NT units, DNA and microtubule imaging showed disarrayed mitotic spindles with misaligned chromosomes, which resulted in unequal chromosome segregation

and aneuploid embryos (page 297, col. 2, parag. 1, lines 5-11). The art, therefore, at the time of filing clearly disclosed the unpredictable nature of nuclear transfer using a primate somatic cell as nuclear donor.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11, 14, 16, 17, 19, 25-30 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kwon et al. (1996) Proced. Natl. Acad. Sci., Vol. 93, pp. 13010-13013.

Kwon teaches the production of mouse embryos and mice by nuclear transfer where a karyoplast or isolated nucleus of metaphase embryo cells was introduced into an enucleated MII phase arrested mouse oocyte, fused and electro-activated, an artificial activation method (page 13010, col. 2, parag. 4, lines 1-3). Embryos were cultured in vitro until the formation of two pronuclei, each of which was then transferred to enucleated fertilized one-cell embryos surrogate mothers for term development (page 13011, col. 1, line 2 to col. 2, line 2-9). The donor genetic material introduced into the oocyte was inherently present in a donor cell prior to removal. Each NT embryo was cultured in vitro to the late 4-cell stage (page 13010, col. 2, parag. 3, lines 1-5). NT embryos were further cultured and underwent cell division after incubation in a surrogate mother as evidenced by development of term mice. Thus, Kwon clearly anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 23 rejected under 35 U.S.C. 103(a) as being unpatentable over Prather et al. (1989) Biology of Reproduction, Vol. 41, pp. 414-418 in view of Kwon et al. (1996) Proced. Natl. Acad. Sci., Vol. 93, pp. 13010-13013.

Prather teaches the production of pig embryos by nuclear transfer, where a nucleus from a pig 2-, 4 or 8-cell embryo was transferred into an enucleated MII arrested pig oocyte and electrofused (page 416, col. 1, parag. 1). One piglet was produced after transfer of 88 (42 + 46; ~1%) reconstructed embryos to a surrogate female pig (page 416, col. 2, lines 3-10).

Kwon teaches the production of mouse embryos by nuclear transfer where a karyoplast or isolated nucleus of metaphase embryo cells was introduced into an enucleated MII phase arrested mouse oocyte, fused and electro-activated, an artificial activation method (page 13010, col. 2, parag. 4, lines 1-3). Kwon teaches 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Prather offers motivation in stating the cell cycle stage of the embryo that is the donor nucleus may be important in successful cloning (page 417, col. 2, lines 3-8). Kwon offers motivation in teaching 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Thus at the time of instant invention, it would have been obvious to the ordinary artisan to modify the method of Prather by synchronizing the cell cycle stage of the donor nuclei to metaphase to match the cell cycle stage of the recipient oocyte given the teachings and motivation of Prather in view of Kwon teaching synchronized donor and reciepient cells

resulted in a 27% success rate over Prather's 1% success rate. The prior art provides the requisite teachings, suggestion and motivation to combine.

Claims 1, 6, 7, 9, 10 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Cibelli et al (1998) Science, Vol. 280, pp. 1256-1258 in view of Kwon et al. (1996) Proced. Natl. Acad. Sci., Vol. 93, pp. 13010-13013.

Cibelli teaches the production of cow embryos by nuclear transfer, where the nucleus of a fibroblast cells transfected with a nucleic acid construct comprising the genes for β-galactosidase and $neo^r$ was inserted into an enucleated MII arrested oocyte (page 1256, col. 3, parag. 1, lines 1-8 and page 1257, col. 1, parag. 2). Of 28 NT embryos transferred to surrogate mothers, 4 calves were born, a success rate of 14%.

Kwon teaches the production of mouse embryos by nuclear transfer where a karyoplast or isolated nucleus of metaphase embryo cells was introduced into an enucleated MII phase arrested mouse oocyte, fused and electro-activated, an artificial activation method (page 13010, col. 2, parag. 4, lines 1-3). Kwon teaches 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Cibelli offers motivation is stating the cell cycle of the donor in the nuclear transfer experiments is unknown, but the properties of the donor cell are important factors (page 1257, col. 3, parag. 3). Kwon offers motivation in teaching 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Thus at the time of instant invention, it would have been obvious to the ordinary artisan to modify the method of Cibelli by synchronizing the cell cycle stage of the donor nuclei to metaphase to match the cell cycle stage of the recipient oocyte given the teachings and motivation of Cibelli in view of Kwon teaching synchronized donor and reciepient cells resulted in a 27% success rate over Cibelli's 14% success rate. The prior art provides the requisite teachings, suggestion and motivation to combine.

Claims 1, 6-10 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Wakayama et al (1998) Nature, Vol. 394, pp. 369-374 in view of Kwon et al. (1996) Proced. Natl. Acad. Sci., Vol. 93, pp. 13010-13013.

Wakayama teaches the production of mouse embryos by nuclear transfer, where the nucleus of a cumulus cell was inserted into an enucleated MII arrested oocyte (page 370, col. 1, parag. 1 to page 371, col. 1, parag. 2 col. 3, parag. 1, line 8). Wakayama teaches about 2-3% success rate in producing mice by nuclear transfer.

Kwon teaches the production of mouse embryos by nuclear transfer where a karyoplast or isolated nucleus of metaphase embryo cells was introduced into an enucleated MII phase arrested mouse oocyte, fused and electro-activated, an artificial activation method (page 13010, col. 2, parag. 4, lines 1-3). Kwon teaches 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Kwon offers motivation in teaching 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Thus at the time of instant invention, it would have been obvious to the ordinary artisan to modify the method of Wakayama by synchronizing the cell cycle stage of the donor nuclei to metaphase to match the cell cycle stage of the recipient oocyte given the teachings and motivation of Wakayama in view of Kwon teaching synchronized donor and reciepient cells resulted in a 27% success rate over Wakayama's 2-3% success rate. The prior art provides the requisite teachings, suggestion and motivation to combine.

Claims 1 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Kwon et al. (1996) Proced. Natl. Acad. Sci., Vol. 93, pp. 13010-13013 in view of Campell et al (1994) Biology of Reproduction, Vol. 50, pp. 1385-1393.

Kwon teaches the production of mouse embryos by nuclear transfer where a karyoplast or isolated nucleus of metaphase embryo cells was introduced into an enucleated

MII phase arrested mouse oocyte, fused and electro-activated, an artificial activation method (page 13010, col. 2, parag. 4, lines 1-3). Kwon teaches 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Campbell teaches the production of reconstructed nuclear transfer sheep embryos by the transfer of a donor cell nucleus into the cytoplasm of enucleated oocyte and activating at the time of transfer (page 1389, col. 1, Table 2). Campbell also teaches the production of nuclear transfer sheep embryos by transfer of a donor cell nucleus into the cytoplasm of an enucleated activated sheep oocyte (page 1390, col. 2, parag. 2, lines 1-4). Campbell offers motivation for using recipient oocytes activated at the time of donor nucleus transfer or preactivated oocytes in stating unactivated MII oocytes contain high levels of MPF which may be detrimental to the develop of the reconstructed embryo (page 1390, col. 2, parag. 1, lines 5-14). Lambs developed from reconstructed embryos transferred to surrogate mother sheep, but percentages are not available. Campbell states the decrease in MPF activity in preactivated or activated at the time of transfer prevents abnormal chromosome number in bovine reconstructed oocytes (page 1391, col. 2, lines 1-6).

Thus at the time of instant invention, it would have been obvious to the ordinary artisan to modify the method of Kwon by using MII oocytes activated at the time of transfer or preactivated in view of Campbell teaching such oocytes give rise to term sheep and in bovines, the percentage of abnormal chromosome number decreases. The prior art provides the requisite teachings, suggestion and motivation to combine.

Claims 1, 11 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwon et al. (1996) Proced. Natl. Acad. Sci., Vol. 93, pp. 13010-13013 in view of Yang et al, (1992) Biol. Reprod. 46, suppl. No. 1, page 117, Abs. 268.

Kwon teaches the production of mouse embryos by nuclear transfer where a karyoplast or isolated nucleus of metaphase embryo cells was introduced into an enucleated

MII phase arrested mouse oocyte, fused and electro-activated, an artificial activation method (page 13010, col. 2, parag. 4, lines 1-3). Kwon teaches 27% of the transferred mouse reconstructed embryos developed to term (page 13012, Table 2).

Yang teaches methods of activating matured oocytes in the presence of cyclohexamide (lines 4-6). Yang teaches that cyclohexamide and electrofusion combined resulted in the activation of 90% of the oocytes (lines 20-27).

Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to supplement electrofusion with electrofusion and cyclohexamide to activate the reconstructed embryos to enhance the rate of embryo formation. The prior art provides the requisite teachings, suggestion and motivation to combine.

Claims 15, 20, 21 and 22 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

August 18, 2006